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## IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Attorney Docket No. Plovlin 2-A  
Wolfgang HEIL et al. : Examiner: L.S. Channavajjala  
Serial No.: 09/757,688 : Group: 1615  
Filed: January 11, 2001 :  
For: DROSPIRENONE FOR HORMONE REPLACEMENT THERAPY

## DECLARATION UNDER 37 C.F.R. §1.132

21/Declaration  
with  
1/132

SIR:

1. I, Ralph Lipp, being duly warned, declare that:
  
2. I am a citizen of Germany, residing in Berlin, Germany.
  
3. I am an inventor of the above-captioned application and am, therefore, familiar with the invention described therein. I am an employee of the assignee, Schering AG, Berlin, Germany. Under German law, I receive royalties from the commercial sale of products covered by this application.
  
4. Please find attached (as Appendix C) my curriculum vitae showing my expertise in the area of pharmaceuticals.
  
5. I have read the Office Action mailed June 26, 2002, from the U.S. Patent and Trademark Office, and the references cited therein.
  
6. I do not consider that one of ordinary skill in the art would have been motivated by

the cited Elliesen (WO 98/11680 and US 5,922,349) or Lignieres (*Clinical Therapeutics* article) or any other prior art of which I am aware to use drospirenone in micronized form for oral administration according to our invention.

7. I respectfully disagree that: a) it would have been obvious to one of ordinary skill in the art at the time the invention was made to employ drospirenone in micronized form, b) micronization of drospirenone would have been expected to increase its rate of dissolution in vitro, c) one of ordinary skill in the art would have been motivated to employ any known pharmaceutical actives in micronized form merely because variations or optimizations of the dosage regimens are considered within the skill of the artisan, or d) one of ordinary skill would have expected *a priori* that micronization would result in increased bioavailability of drospirenone.

8. Bioavailability of a drug is affected by many factors. Merely providing a drug in a form which exposes more available surface area of the drug cannot reasonably be expected to increase bioavailability or otherwise be advantageous in all cases. Micronization in many cases increases the solubility of a drug, but this is not true in all cases. (See, e.g., Appendix B, References 1 and 2). Moreover, solubility and bioavailability do not necessarily correspond. When drugs are subject to degradation in an environment upon dissolution, for example, in the gastric (acidic) environment for orally administered drugs, increasing their solubility would logically be expected to lessen bioavailability.

9. Some drugs have instability in certain environments which leads to their degradation, e.g., conversion to inactive derivatives, isomers, etc. Such drugs may need to be protected from destabilizing environments so that degradation is prevented or limited until they reach

an environment in which they are stable and can become bioavailable more effectively. For example, the reported low bioavailability of etoposide upon oral administration was thought to be due, at least in part, to chemical instability at pH 1.3, i.e., the typical acidic pH in the human stomach. Etoposide has a degradation half-life of about 2.9 hours at pH 1.3. See attached Appendix B, Reference 3.

10. References 1-2 and 4-10 in Appendix B show that micronization of other drugs does not necessarily lead to increased bioavailability over other forms or can be detrimental to bioavailability.

11. It is well known in the art that orally administered drospirenone has to pass through the stomach and into the intestine to be taken up in a bioavailable manner but one of ordinary skill in the art knew that drospirenone was a drug which had instability in acidic media, i.e., it isomerizes to an inactive form under conditions well known to exist in the acidic stomach. See Nickisch et al., Tetrahedron Letters, vol. 27, no. 45, pp. 5463-5466 (1986), translated copy attached. On page 2 of the translation, it is shown that the isomerization results in predominantly (8:2 ratio) the inactive isomerization product in a pH 1 environment such as the stomach. We have further demonstrated that micronized drospirenone has a short degradation/isomerization half-life of about 30 minutes at pH 1, i.e., the isomerization is fast. See attached Appendix A, part 1, showing that when micronized drospirenone is exposed to an acidic environment of pH 1, in vitro, about 50% of the active form of drospirenone is isomerized to its inactive form within 31 minutes. Thus, if providing drospirenone for oral administration in micronized form could have been expected to increase its surface area and thus exposure to its environment, as suggested by the Examiner in the Office Action, such increased exposure would have been expected by one of ordinary skill in the art to expose

more of the drospirenone to rapid isomerization to its inactive form in the stomach. See also Figure 1 of the related application Ser. No. 09/654,227 for a comparison of the *in vitro* dissolution profiles for micronized (curves V1-V7) versus macrocrystalline (curve V8) drospirenone. Accordingly, one of ordinary skill in the art would not have been motivated to provide orally administrable doses of drospirenone in micronized form, as recited in the claims of the above-captioned application.

12. In summary, based on the above-established facts, one of ordinary skill in the art could not have been motivated to provide and use drospirenone in micronized form as a drug for oral administration. There would have been no reasonable expectation by one of ordinary skill in the art that micronization would increase its bioavailability. The teachings in the art that some drugs can be advantageously administered in micronized form would not be considered by one of ordinary skill in the art to be applicable to all drugs, particularly not to drugs as acid sensitive as drospirenone, especially in view of its known isomerization to an inactive form under acidic conditions. Thus, one of ordinary skill in the art would not have been motivated to modify the teachings of the prior art – including the cited Elliesen and Lignieres references – to micronize drospirenone.

13. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: March 7, 2003Signed: Ralph Lipp  
Dr. Ralph Lipp

**APPENDIX A**

The half-life of micronized drospirenone during dissolution testing at various pH values is presented. The definition of the half-life relates to the time after which the starting concentration of the active form of micronized drospirenone is reduced to 50% because of isomerization into its non-active isomer.

**Results:**

pH value	Half-life of micronized drospirenone
1	31 min
2	4.7 h
3.5	$\approx$ 50 h
5	$\approx$ 75 h
7	$\approx$ 75 h

The data clearly indicate that the micronized drospirenone is dramatically degraded at low pH values present in the gastric environment. This would direct the person of skill in the art away from orally administering micronized drospirenone.

**APPENDIX B****1. Development of a new tablet formulation of theophylline: In vitro and in vivo studies;**

Montel et al.; *Drug Development and Industrial Pharmacy*, (vol. 9 (3), pp. 399-420, 1983.

**Abstract**

"Studies on dissolution rate showed that the release of theophylline from tablet A (theophylline of commercial quality) and tablet B (theophylline of selected particle size) was faster than from tablet C (micronized theophylline)... The in vivo study showed that only tablet B has the same bioavailability as an aqueous solution, whilst bioavailability of tablet A and tablet C was lower than that of tablet B and the aqueous solution."

**2. Dissolution properties and in vivo behavior of triamterene in solid dispersions with**

**polyethylene glycol**; Arias et al; Abstract of *Pharm-Acta-Helv.*, (vol. 71, no.4, pp. 229-235 (1996)).

**Abstract**

"Relative bioavailability...was greater for all of the solid dispersions than micronized triamterene."

"Dissolution efficiency in 30 min. (DE30) increased from 9.84% for micronized triamterene to 18.5-58.2% for physical mixtures and to 25.26 to 86.17% for solid dispersions."

3. Preformulation study of etoposide: Identification of physicochemical characteristics responsible for the low and erratic oral bioavailability of etoposide; Shah et al.; Abstract of *Pharmaceutical Research*, vol. 6, 408-412, May 1989.

Abstract

"It was concluded that the low equilibrium aqueous solubility, slow intrinsic dissolution rate and chemical instability at pH 1.3 may account for the low oral bioavailability."

4. Phase I and pharmacokinetic study of micronized formulation of carboxyamidotriazole, a calcium signal transduction inhibitor: toxicity, bioavailability and the effect of food; Berlin et al.; Abstract of *Clinical Cancer Research*, 2002, Vol. 8(1); pp. 86-94.

Abstract

"The micronized formulation was absorbed more slowly than the gelcap formulation."

5. Efficacy and safety of reformulated, micronized glyburide tablets in patients with non-insulin dependent diabetes mellitus: a multicenter, double-blind, randomized trial; Carlson et al.; Abstract of *Clinical Therapeutics*, 1993, Vol. 15(5), 788-96.

Abstract

"In a double-blind 12-week study, the subjects were randomly assigned to continue receiving 5-mg tablets of original [non-micronized] glyburide [in doses of 5, 10, 15, or 20 mg daily] or to substitute 3-mg tablets of reformulated, micronized glyburide .... Glyburide tablets had been reformulated [by micronization of the active agent] to

improve their bioavailability... The differences [in serum glucose levels] between groups were not significant."

6. About a Pharmacokinetic Study of Progesterone in Comelts; Duclos et al., Abstract of *Eur. J. Metab. Pharmacokinetic*; 15(2), Suppl., Abstr.226, 1990.

Abstract

"In vitro dissolution rate of progesterone was faster from PEG 600 solid dispersions than from micronized progesterone."

"...solid dispersions gave higher Cmax, earlier Tmax, and increased 8-hour AUC."

7. Bioavailability of griseofulvin from a novel capsule formulation; Fell et al.; Abstract of *The Journal of Pharmacy and Pharmacology*, 1978, 30(8), 479-82.

Abstract

"The in vivo availability of griseofulvin from a novel formulation has been compared with the micronized powder....The results of the in vivo study show the formulation technique has increased the rate and extent of bioavailability of griseofulvin when compared with non-treated (micronized) powder."

8. Lyophilized Preparations of Griseofulvins. 2nd Communication. In vivo release; Froemming et al.; Abstract of *Pharm. Ind.*, 48(7), 1986, 837-40.

Abstract

"Bioavailability of p.o. freeze-dried griseofulvin (GF) was greater than that of ... micronized GF."

9. Comparison of galenic formulations of orlistat (tetrahydrolipstatin). A pharmacological approach. Hartmann et al., Abstract of *Drug Investigation*, 1993, 5(1), 44-50.

Abstract

"...capsule formulations containing orlistat as micronized powder (A) or granules (B) were compared using the following pharmacological end-points..."; "At the 150 mg dose (B) showed a trend toward superior efficacy compared with (A)."

10. Pharmacokinetics and bioavailability of diltiazem. Kohno et al., Abstract of *Arzneimittel Forschung*, 1977, 27(7), 1424-1428.

Abstract

"In the bioavailability study, a comparison of plasma concentrations of diltiazem between the two different crystals and the micronized powder resulted in no difference in their bioavailability."

## Appendix C

### Curriculum Vitae for Priv. -Doz. Dr. Ralph Lipp

Born: 12 May 1960 in Weiterstadt, Germany

German citizen

Married, two children

#### Basic studies

1966-79 Elementary and high school

June 1979 High school Graduate

#### Military service

July 1979-

September 1980 Basic military service

#### Higher education

1980-84 Pharmaceutical Chemistry studies at the University of Mainz

1984 Practical studies in Pharmacy in Weiterstadt

84-85 Practical studies in Röhm Pharma, Weiterstadt

85 Pharmacist graduate

February 1990 Graduation as Doctor in Natural Science at the Free University of Berlin under the guidance of Prof. Dr. Dr. Dr. h. c. W Schunack

2000 International Executive program, INSEAD, Fontainbleau, France

2001 Lecturing exam at the Department of Pharmaceutical Technology at the University of Berlin

2001 Advanced Management Program at Harvard University

#### Employment Record

85-90 Researcher at the Free University of Berlin in "Instrumental Analysis" and "Drug Formulation"

90-96 Leader of the scientific work group "Dermal and Transdermal Drug Substance Applications" at Schering AG

Since April 1992 Teachers representative at the Department of Pharmaceutical Technology at the Free University of Berlin

96-98 Head of the group "Drug delivery systems- transdermal systems" at Schering  
97-2001 Head of Oral Dosage Forms at Schering  
Since June 1999 Production manager for clinical test products at Schering AG  
Since 2001 Head of Pharmaceutical Development at Schering AG

### **Professional memberships**

INSEAD  
Harvard  
Member of the German Pharmaceutical chemist's society  
and another pharmacist's society

### **List of publications**

#### **Posters and lectures**

1. J. Kleine-Tebbe, M. Bolz, R. Lipp, W. Schunack and G. Kunkel, *Presence of histamine-H<sub>3</sub>-receptors on human basophils*, Poster, New Engl. Reg. Allergy Proc. 9, Abstract 276 (1988).
2. R. Lipp, W. Schunack, J.-M. Arrang, M. Garbarg and J.-C. Schwartz, *Synthesis and H<sub>3</sub>-antagonistic activity of N<sup>α</sup>-substituted histamine derivatives*, 10th International Symposium on Medicinal Chemistry, Poster, Abstract P-119, Budapest (Hungary), 15.-18.8.1988.
3. J. Kleine-Tebbe, J. Schramm, R. Lipp, W. Schunack and G. Kunkel, *Influence of histamine-H<sub>3</sub>-antagonists on human leukocytes*, 18th Meeting of the European Histamine Research Society, Poster, Abstract 119, Breda (Netherlands), 17.-20.5.1989.
4. W. Schunack, S. Elz, F. Keller and R. Lipp, *Chirale Agonisten und Antagonisten des Histamin H<sub>2</sub>- und H<sub>3</sub>-Rezeptors*. 7. Symposium "Potentielle Arzneistoffe", Lecture, Erfurt (Germany), 24.-26.4.1990.
5. H. Stark, R. Lipp, W. Schunack, J.-M. Arrang, N. Defontaine and J.-C. Schwartz, *Structural variations outgoing from N<sup>α</sup>-acylated histamine derivatives and their influence on H<sub>3</sub>-antagonistic activity*, New Perspectives in Histamine Research, Satellite symposium of the XIth International Congress of Pharmacology of IUPHAR, Poster, Noordwijkerhout (Netherlands), 6.-8.7.1990.
6. J.-M. Arrang, M. Garbarg, J.-C. Schwartz, R. Lipp, H. Stark, W. Schunack and J.-M. Lecomte, *The histamine H<sub>3</sub>-receptor: Pharmacology, roles and clinical implications*

*studied with agonists*, New Perspectives in Histamine Research, Satellite symposium of the XIth International Congress of Pharmacology of IUPHAR, Lecture, Noordwijkerhout (Netherlands), 6.-8.7.1990.

7. R. Lipp, J.-M. Arrang, J. Buschmann, M. Garbarg, P. Luger, W. Schunack and J.-C. Schwartz, *Novel chiral H<sub>3</sub>-receptor agonists*, New Perspectives in Histamine Research, Satellite symposium of the XIth International Congress of Pharmacology of IUPHAR, Lecture, Noordwijkerhout (Netherlands), 6.-8.7.1990.
8. J. Kleine-Tebbe, J. Schramm, M. Bolz, H. Gagné, C. Josties, R. Lipp, A. Friese, H. Stark, V. Zingel, A. Buschauer, W. Schunack and G. Kunkel, *Influence of histamine H<sub>1</sub>-, H<sub>2</sub>-, H<sub>3</sub>-(ant)agonists on IgE-mediated histamine release from human basophils*, Poster, International Allergy Congress, München (Germany), 1990.
9. H. Stark, R. Lipp, W. Schunack, J.-M. Arrang, N. Defontaine and J.-C. Schwartz, *Synthese und Aktivität neuer Histamin H<sub>3</sub>-Antagonisten*, Scientific congress of the Deutsche Pharmazeutische Gesellschaft (German Pharmaceutical Society), Poster, PA19, Berlin (Germany), 8.-12.9.1990; Arch. Pharm. (Weinheim) 323, 729 (1990).
10. R. Lipp, J.-M. Arrang, J. Buschmann, M. Garbarg, P. Luger, W. Schunack and J.-C. Schwartz, *Synthese, Molekülstruktur and H<sub>3</sub>-agonistische Aktivität seitenkettenverzweigter Histamine*, Scientific congress of the Deutsche Pharmazeutische Gesellschaft (German Pharmaceutical Society), Lecture, DA32, Berlin (Germany), 8.-12.9.1990; Arch. Pharm. (Weinheim) 323, 658 (1990).
11. H. Stark, R. Lipp, W. Schunack, J.-M. Arrang, M. Garbarg and J.-C. Schwartz, *H<sub>3</sub>-Activity of alkylated histamine derivatives*, XXth Meeting of the European Histamine Research Society, Poster, P44, Marburg (Germany), 9.-12.5.1991.
12. H. Stark, R. Lipp, W. Schunack, J.-M. Arrang, M. Garbarg, J.-C. Schwartz, *Pharmacochemistry and histamine H<sub>3</sub>-activity of alkylhistamines*, United Congress of the French and German Pharmaceutical Societies, Straßburg, France, 19.-22.9.1991.
13. H. Stark, J.-M. Arrang, M. Garbarg, A. Roleau, J.-M. Lecomte, R. Lipp, J.-C. Schwartz and W. Schunack, *Prodrugs of histamine H<sub>3</sub>-agonists for improved drug penetration through blood-brain barrier*, XIIth International Symposium on Medicinal Chemistry, Basel (Switzerland), 13.-17.9.1992.
14. H. Stark, J.-M. Arrang, M. Garbarg, A. Roleau, J.-M. Lecomte, R. Lipp, J.-C. Schwartz and W. Schunack, *Prodrug approach for histamine H<sub>3</sub>-agonists*, 1st European Congress of Pharmaceutical Sciences, Amsterdam (Netherlands), 7.-9.10.1992.
15. H. Stark, R. Lipp, J.-M. Arrang, M. Garbarg, A. Rouleau, J.-C. Schwartz and W. Schunack, *New histamine H<sub>3</sub>-agonistic componads penetrating into CNS*, XXIInd Annual Meeting of the European Histamine Research Society, Poster, P72, Köln (Germany), 19.-22.5.1993.

16. R. Lipp, *Selection and use of crystallization inhibitors for steroid loaded transdermal delivery systems*, 40th Annual Meeting of the APV, Lecture, Abstract 114, Mainz (Germany), 9.-12. 3. 1994; *Eur. J. Pharm. Biopharm.* 40 (Suppl.), 85 (1994).
17. R. Lipp, J. Riedl, A. Sachse and T. Schneider, *Cyproteron acetate-containing liposomes for topical application*, 2nd European Congress of Pharmaceutical Sciences, Lecture, FC6, Berlin (Germany), 29.9.-1.10.1994; *Eur. J. Pharm. Sci.* 2, 102 (1994).
18. R. Lipp and A. Müller-Fahrnow, *X-ray structure determinations of crystals grown in transdermal delivery systems containing estradiol or gestodene*, American Association of Pharmaceutical Scientists Ninth Annual Meeting, Poster, PDD 7154, San Diego (CA, U.S.A.), 6.-10.11.94; *Pharm. Res.* 11, S-213 (1994).
19. C. Günther, R. Lipp, J. Riedl and U. Täuber, *In vitro studies on the percutaneous absorption of Lisuride*, Prediction of Percutaneous Penetration - Methods Measurements Modeling, Poster, La Grande Motte (France), 2.4.-6.4.1995.
20. C. Günther, R. Lipp, T. Mager, J. Riedl and U. Täuber, *Percutaneous absorption of lisuride in man*, Prediction of Percutaneous Penetration - Methods Measurements Modeling, Oral Poster, La Grande Motte (France), 2.4.-6.4.1995.
21. R. Lipp, H. Laurent, C. Günther, J. Riedl, P. Esperling and U. Täuber, *Rational Design of Prodrugs for Matrix-type Transdermal Delivery Systems: Gestodene Esters*, Symposium on Controlled Release of Bioactive Materials, Seattle 1995, Poster; Proceed. Intern. Symp. Control. Rel. Bioact. Mater., 22, 672 (1995).
22. R. Lipp, *Neue technologische Konzepte für die Entwicklung sexualsteroidhaltiger Transdermalsysteme*, Lecture, Freie Universität Berlin, Berlin (Germany) 1995.
23. R. Lipp, *Transdermal Drug Delivery Systems*, Lecture within the seminar: *Medical Adhesives: Technology and Applications*, Zürich (Switzerland), 2. - 4.12.1996.
24. R. Lipp, *Transdermal Drug Delivery Systems*, Lecture within the seminar: *Medical Adhesives: Technology and Applications*, Basel, (Switzerland) 27.-29.10.1997.
25. R. Lipp and C. Günther, *Use of Dimethylisosorbide to enhance the transdermal fluxes of sex steroids from polyacrylate based matrix TDSS*, American Association of Pharmaceutical Scientists 13th Annual Meeting, Poster, San Diego (CA, U.S.A.), 15.-19.11.1998; *Pharm. Sci.* 1, (1998).
26. A. P. Funke, C. Günther, R. H. Müller and R. Lipp, *Low-frequency sonophoresis of methyl nicotine at physiological skin temperature*, Poster, PPP-MMM-Conference, 2000.
27. R. Lipp, *Zukunftsweisende Darreichungsformen für Proteine und Peptide*, Lecture, Freie Universität Berlin, Berlin (Germany) 12.02.2001.
28. R. Lipp, *Fortschritte bei steroidhaltigen Drug Delivery Systemen*, Lecture, German Pharmaceutical Society, Berlin (Germany) 25.10.2001.

29. P. Lienau, T. Backensfeld, W. Weitschies and R. Lipp, *The use of phasediagrams in the formulation of self micro-emulsifying systems (SMES) with different types of nonionic surfactants*, Poster, 4<sup>th</sup> World Meeting on Pharmaceutics, Biopharmaceutics and Pharmaceutical Technology, Florence (Italy) 08.04.-11.04.2002.

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2. J. Altman, M. Wilchek, R. Lipp and W. Schunack, *An improved synthesis of L-homohistidine*, *Synth. Comm.* 19, 2069 (1989).
3. J.-M. Arrang, M. Garbarg, W. Schunack, J.-C. Schwartz and R. Lipp, *Dérivé de l'histamine, sa préparation et son application en thérapeutiques*, Demande de brevet européen (Europ. patent application) 4 767 778 (25.10.89).
4. R. Lipp, *Liganden des Histamin-H<sub>3</sub>-Rezeptors - Synthese und Wirkung von Imidazolylalkanaminen and Derivaten*, PhD thesis, Freie Universität Berlin, Berlin (Germany), 1990.
5. J. Kleine-Tebbe, J. Schramm, R. Lipp, W. Schunack and G. Kunkel, *Influence of histamine-H<sub>3</sub>-antagonists on human leukocytes*, *Agents Actions* 30, 137-139 (1990).
6. H. Stark, R. Lipp, W. Schunack, J.-M. Arrang, N. Defontaine and J.-C. Schwartz, *Structural variations outgoing from N<sup>α</sup>-acylated histamine derivatives and their influence on H<sub>3</sub>-antagonistic activity*, *Agents Actions Suppl.* 33, in "New Perspectives in Histamine Research", H. Timmerman and H. van der Goot (Editor), Birkhäuser Verlag, Basel - Boston - Berlin, 1991.
7. J.-M. Arrang, M. Garbarg, J.-C. Schwartz, R. Lipp, H. Stark, W. Schunack and J.-M. Lecomte, *The histamine H<sub>3</sub>-receptor: Pharmacology, roles and clinical implications studied with agonists*. *Agents Actions Suppl.* 33, in "New Perspectives in Histamine Research", H. Timmerman and H. van der Goot (Editor), Birkhäuser Verlag, Basel - Boston - Berlin, 55-67, 1991.
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9. J. Kleine-Tebbe, J. Schramm, M. Bolz, H. Gagné, C. Josties, R. Lipp, A. Friese, H. Stark, V. Zingel, A. Buschauer, W. Schunack and G. Kunkel, *Influence of histamine H<sub>1</sub>, H<sub>2</sub>-, H<sub>3</sub>-(ant)agonists on IgE-mediated histamine release from human basophils*,

in "New Trends in Allergy III", J. Ring and B. Przybilla (Editor), Springer Verlag, Berlin - Heidelberg, 152-157, 1991.

10. M. Garbarg, J.-M. Arrang, W. Schunack, R. Lipp, H. Stark, J.-M. Lecomte and J.-C. Schwartz, *Novel histamine H<sub>3</sub>-receptor agonist compounds for therapeutic use, pharmaceutical compositions acting as agonist of said receptor and method of preparation*, WO 91/17146 (14.11.1991); US patent 5342960 (30.8.1994).
11. M. Garbarg, J.-M. Arrang, C. Llorens-Cortes, H. Pollard, A. Roleau, J.-C. Schwartz, M. D. Trung Tuong, R. Lipp, H. Stark, W. Schunack and J.-M. Lecomte, *Autoreceptors and heteroreceptors evidenced by histamine H<sub>3</sub> receptor ligands*, in "Advances in the biosciences", Vol. 82 der Reihe: Presynaptic receptors and neuronal transporters, A. M. Galzin and J. Constantin (Editor), Pergamon Press, Oxford, 67-70, 1992.
12. R. Lipp, H. Stark and W. Schunack, *Pharmacochemistry of histamine H<sub>3</sub>-receptors*, in "The histamine receptor", J.-C. Schwartz and H. L. Haas (Editor), Wiley-Liss Inc. New York, 57-72, 1992.
13. J. Riedl, C. Günther and R. Lipp, *Mittel zur transdermalen Applikation enthaltend Ergolin-Derivate*, German patent application DE 4 116 912 (26.11.1992).
14. R. Lipp, J.-M. Arrang, M. Garbarg, P. Luger, J.-C. Schwartz and W. Schunack, *Synthesis, absolute configuration, stereoselectivity, and receptor selectivity of (αR,βS)-α,α-dimethylhistamine, a novel highly potent histamine H<sub>3</sub> receptor agonist*, J. Med. Chem. 35, 4434-4441 (1992).
15. J. Riedl, R. Lipp and M. Hartisch, *Transdermale Therapeutische Systeme mit Penetrationsverstärkern*, German patent application DE 4 210 165 (4.2.1993).
16. R. Lipp, J. Riedl and J. W. Tack, *Transdermale Therapeutische Systeme mit Kristallisationsinhibitoren*, WO 93/08795 (13.5.1993).
17. J.-C. Schwartz, J.-M. Arrang, M. Garbarg, J.-M. Lecomte, C. R. Ganellin, A. Fkyerat, W. Tertiuk, W. Schunack, R. Lipp, H. Stark and K. Purand, *Nouveaux dérivés de l'imidazole, leur préparation et leurs applications thérapeutiques*, French patent application FR 2 686 084 - A1 (16.7.1993).
18. R. Lipp, C. Günther, J. Riedl and U. Täuber, *Transdermal application agent containing 3-Keto-Desogestrel*, International patent application WO 94/04157 (3.3.1994).
19. C. Günther, R. Lipp, U. Täuber and J. Riedl, *Transdermal application agent containing 14a,17a-Ethanoestra-1,3,5(10)-trien-3,17β-diol*, German patent application DE-A 4 240 806 (9.6.1994).
20. H. Stark, R. Lipp, J.-M. Arrang, M. Garbarg, J.-C. Schwartz and W. Schunack, *Acylated and alkylated histamine derivatives as new histamine H<sub>3</sub>-receptor antagonists*, Eur. J. Med. Chem. - Chim. Ther. 29, 695-700 (1994).

22. R. Lipp, H. Laurent, C. Günther, J. Riedl, P. Esperling and U. Täuber, *Mittel zur transdermalen Applikation enthaltend Gestodenester*, International patent application WO 95/05827 (2.3.1995).
23. R. Lipp, H. Stark, J.-M. Arrang, M. Garbarg, J.-C. Schwartz and W. Schunack, *Synthesis and histamine H<sub>3</sub>-receptor activity of mono- and dialkyl substituted histamine derivatives*, Eur. J. Med. Chem. - Chim. Ther., 30, 219-225 (1995).
24. H. Stark, R. Lipp, J.-M. Arrang, M. Garbarg, X. Ligneau, J.-C. Schwartz and W. Schunack, *New potent histamine H<sub>3</sub>-receptor antagonists of the amide type*, Eur. J. Pharm. Sci. 3, 95 (1995).
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